REMARKS

Reconsideration and allowance are respectfully requested.

Claims 22 and 23 have been amended. New claim 25 has been added. The amendments are for the sake of clarity only, and add no new matter. The amendments were made to make clear that the claims encompass only conjugates of a polypeptide consisting of the amino acid sequence set forth in SEQ ID NO:2 and a single branched poly(ethylene glycol) group, where the branched poly(ethylene glycol) group can be attached to the polypeptide via either cysteine 110 or cysteine 117, and mixtures of these species (i.e., a mixture of cysteine 110 and cysteine 117 singly-attached PEG species). Claim 25 specifically claims the mixture.

This amendment is made in response to the Examiner's assertion on page 5, second paragraph of the Office Action of January 21, 2010, in which he stated that the pending claims "...encompass conjugates that are PEGylated at other sites or are PEGylated at both cysteine 110 and cysteine 117 and no evidence or scientific reasoning has been presented to establish that any of the properties of the conjugate species taught would be shared by the other conjugate species broadly encompassed by the claims."

It is respectfully submitted that the amendments to the claims make clear that the claims do NOT encompass any species that are not PEGylated at one or the other of cysteines 110 and 117. The claims do encompass a mixture of the PEGylated species.

The Rejections Under 35 U.S.C. § 103(a)

Amended claims 22 to 24 and new claim 25 all include the limitation that the conjugate must be PEGylated at cysteine 110 or 117 by a branched, 40 kDa PEG group, or must be a mixture of such species. An example of such a mixture is specifically disclosed in the specification (see, e.g., Example 5, page 22, lines 6 to 12).

Applicants have submitted herewith the Declaration Under 37 C.F.R. 1.132 of Dr. Kurt Lang, one of the inventors of the present claims, which establishes the unexpectedly superior properties of the 40 kDa PEGylated IGFBP-4. Dr. Lang's declaration discusses the data demonstrating the unexpected superiority of the 40 kDa PEGylated IGFBP-4 over unPEGylated and 20 kDa PEGylated IGFBP-4. Upon information and belief, it is the mixture of species which is employed in the Examples from the specification which are referred to in Dr. Lang's declaration.

The experimental details from which the data are derived are set forth in Examples 13, 14 and 15 of the above-captioned application, entitled "Serum Kinetics of IGFBP-4 Derivatives", "Antitumorigenic Effect of IGFBP-4 Derivatives in the PancTu-1 Orthotopic Pancreas Cancer Model" and "Influence of PEGylated IGFBP-4 on Normal Kidney Cells/Kidney Organs," respectively.

The results for the Example 13 showed that by daily application of IGFBP-4, monoPEG20-IGFBP-4, and monoPEG40-IGFBP-4 to mice only monoPEG40-IGFBP-4 accumulated in serum.

The results for the Example 14 showed that:

(1) both tumor markers assayed (CA19.9 and Cyfra 21.1) were significantly reduced by treatment with monoPEG40-IGFBP-4 but not by treatment with monoPEG20-IGFBP-4; and that

(2) chronic administration of monoPEG20-IGFBP-4 did not inhibit tumor growth, as it was found that mean tumor volume at termination was 287 mm3 and very similar to the control group receiving only PBS (226 mm3) whereas in contrast, treatment with monoPEG40-IGFBP-4 reduced tumor growth, with mean tumor volume calculated at 163 mm3 for the monoPEG40-IGFBP-4 treatment group. The CA19.9 and Cyfra 21.1 tumor marker results are shown in tabular form in Tables 2 and 3 on page 29 of the application as filed and on page 10 as published.

The results for Example 15 showed that chronic treatment with mono-20 kDa-PEG-IGFBP-4 applied s.c. or i.p. induced moderate to severe histopathological alteration of kidney tissue. Cells belonging to proximal tubules were vacuolated without sign of inflammation and necrosis. These findings were not observed after s.c. or i.p. application of mono-40 kDa-PEG-IGFBP-4.

Based upon the foregoing, Dr. Lang concluded that:

(1) that only with a monoPEG40-IGFBP-4 therapeutically effective serum levels can be obtained, and

(2) that only with monoPEG40-IGFBP-4 a reduction of the tumor markers CA19.9 and Cyfra 21.1 can be seen, and

(3) that with monoPEG20-IGFBP-4 severe histopathological alterations of kidney tissue are induced.

Dr. Lang further states that these findings were absolutely surprising as the in vitro binding experiments showed that IGFBP-4 and monoPEG20-IGFBP-4 as well as monoPEG40-IGFBP-4 showed IGF-binding and inhibition of IGF-I receptor phosphorylation whereas only monoPEG40-IGFBP-4 showed also an effect in vivo which in contrast was not seen for monoPEG20-IGFBP-4. At the same time it was also surprising that monoPEG20-IGFBP-4 did not accumulate in blood serum whereas monoPEG40-IGFBP-4 did. And finally most surprisingly and absolutely unexpected was that monoPEG20-IGFBP-4 caused severe histopathological changes in kidney tissue which were not observed for monoPEG40-IGFBP-4.

To the extent the Examiner asserts that these surprising advantages of the claimed compositions are not recited in the claims, it is respectfully submitted that this is not required. "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

Thus, none of the cited references discloses or suggests that an IGFBP-4 PEGylated with a branched PEG residue of about 40 kDa has the superior properties relative to 20 kDa PEGylated IGFBP-4 as reported in the examples of the present application, and in particular none of the cited references provide any expectation that a 40kDa PEGylated IGFBP-4 would be less toxic than a conjugate with a 20 kDa PEG residue, as is demonstrated by the data in the present application.

As previously noted, the Examiner also acknowledges that there are "...multiple different species of PEG polymer..." available to those of ordinary skill in the art. None of the cited references points to the use of a PEG polymer that would result in the claimed compound, as the PEG reagent of Veronese is an amine-specific reagent, while the claimed compounds are PEGylated at cysteines. Following the teachings of Veronese, one might have tried to attach branched 40 kDa PEG to a free amino group of IGFBP-4, but would have had no reason to attempt to attach at cysteines, and would have absolutely no reason to expect that the resulting claimed molecule would have the superior properties that it possesses. None of the cited art discloses a branched 40 kDa PEG reagent suitable for coupling to free thiols, as would be required to achieve the compound of the claims.

In light of the above arguments, amendments, and the declaration of Dr. Lang, it is respectfully submitted that the newly submitted claims are in condition for allowance, and such action is earnestly solicited.

The fee for a one-month extension of time is submitted with this amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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